Thresholds - Definitions, Data Collection, Limitations and Harmonization

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Why are we interested in Thresholds?

- Very small amounts of specific allergens can provoke reactions in some individuals, but
  - we don’t know in how many
  - we don’t know how small the amounts are
  - we don’t know how severity of reaction relates to an individual’s sensitivity
  - allergic people are known to react differently on different occasions

So it is difficult to assess how much needs to be done to achieve the desired level of safety with respect to allergens.

Source: R. Crevel, IUFoST - Chicago, July 2003
Historical Approach to Dose/Response

- Physicians recommended completed avoidance (ZERO threshold)
- Ingestion of small amounts (not well defined) could elicit allergic reactions
- DBPCFC was the gold standard for diagnosis but challenges often started at 400 – 500 mg
- 20%+ of patients reacted to first challenge dose – some severe rxns
Historical Approach to Dose/Response

- Peanut-allergic consumers have practiced complete avoidance (zero threshold)
- Peanut-allergic consumers still experienced occasional allergic reactions (hidden ingredients, cross contact, FOOD SERVICE)
- Unexpected allergic reactions to peanuts were occasional severe leading to widespread belief that low doses elicited severe reactions
Status of Dose/Response Knowledge circa 2005

- Trace amounts (low mg) can elicit allergic reactions
- Severity of response is related directly to dose (even that might not be universally held opinion)
- Individuals vary in degree of sensitivity
- How much is too much?
- A few clinics started doing very low dose DBPCFC and proved that safe doses exist for every subject and that severe reactions did not occur at very low doses (low mg)

Our 1st indication of safe doses
Current Situation

- Public health authorities have not established regulatory thresholds for allergenic foods
- U.S. FALCPA – de facto zero threshold for source labeling of ingredients
- Many regulatory authorities establish zero threshold for undeclared allergen
- Industry acutely aware of allergens, no guidance on thresholds so rampant use of precautionary labeling
**Baking Soda**

**Nutrition Facts**

**Serving Size:** 1/8 tsp (0.6g)

**Servings Per Container:** about 378

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>0g</td>
</tr>
<tr>
<td>Calories from Fat</td>
<td>0g</td>
</tr>
<tr>
<td>Total Fat</td>
<td>0g</td>
</tr>
<tr>
<td>Saturated Fat</td>
<td>0g</td>
</tr>
<tr>
<td>Trans Fat</td>
<td>0g</td>
</tr>
<tr>
<td>Polyunsaturated Fat</td>
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</tr>
<tr>
<td>Monounsaturated Fat</td>
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<tr>
<td>Cholesterol</td>
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<tr>
<td>Sodium</td>
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</tr>
<tr>
<td>Potassium</td>
<td>0mg</td>
</tr>
<tr>
<td>Total Carbohydrate</td>
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</tr>
<tr>
<td>Dietary Fiber</td>
<td>0g</td>
</tr>
<tr>
<td>Sugars</td>
<td>0g</td>
</tr>
<tr>
<td>Protein</td>
<td>0g</td>
</tr>
</tbody>
</table>

Folic Acid 0%

Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

<table>
<thead>
<tr>
<th>Calories</th>
<th>2,000</th>
<th>2,500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Fat</td>
<td>Less than 65g</td>
<td>80g</td>
</tr>
<tr>
<td>Sat Fat</td>
<td>Less than 20g</td>
<td>25g</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Less than 300mg</td>
<td>300mg</td>
</tr>
<tr>
<td>Sodium</td>
<td>Less than 2,400mg</td>
<td>2,400mg</td>
</tr>
<tr>
<td>Potassium</td>
<td>3,500mg</td>
<td>3,500mg</td>
</tr>
<tr>
<td>Total Carbohydrate</td>
<td>Less than 300g</td>
<td>375g</td>
</tr>
<tr>
<td>Dietary Fiber</td>
<td>25g</td>
<td>30g</td>
</tr>
</tbody>
</table>

**INGREDIENTS:** SODIUM BICARBONATE

**ALLERGY WARNING:** MANUFACTURED IN A FACILITY THAT PROCESSES MILK, EGGS, WALNUTS, PEANUTS, WHEAT, SOYBEANS.

**MARKETED BY:** Wal-Mart Stores, Inc.
Bentonville, AR 72716
©2000
Current Situation

• Quality of life for food-allergic consumers suffers partially as a result of difficulties in adherence to avoidance diets
• Food-allergic consumers increasingly ignore products with precautionary labels
• Some physicians advise food-allergic patients to avoid precautionary labels
• Allergic reactions continue to occur but rarely with packaged foods
US FDA Allergen Thresholds

- Threshold Working Group Report
- “Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food” (March, 2006)

Terminology

- NOAEL – the No Observed Adverse Effect Level
- NOAEL – the maximum tolerated dose that produces no symptoms as determined by oral clinical challenge trials in food-allergic subjects
- LOAEL – the Lowest Observed Adverse Effect Level
- LOAEL - the minimal eliciting dose as determined by oral clinical challenge trials in food-allergic subjects

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10
Terminology

• Individual Threshold – LOAEL or NOAEL for an individual patient
• Population Threshold – LOAEL or NOAEL for a group of food-allergic individuals e.g.
  - all peanut-allergic individuals
  - peanut-allergic individuals in a particular clinic or group/sub-group
Terminology

• In reality, an individual’s personal threshold lies somewhere between their NOAEL and LOAEL

• Interval Sensoring Survival Analysis
  - assigns equal probability that the true threshold dose could fall anywhere on the continuum from NOAEL to LOAEL
Terminology – What Constitutes a Reaction?

- A response that poses a risk to human health
  - Regulatory view under U.S. FALCPA

- The first response of any type including mild, subjective (cannot be confirmed by physician or other observer), transitory responses

- The first objective response that can be visually observed by a physician or other observer (also usually mild and transitory if oral challenges started at sufficiently low dose

- An objective response that meets some defined criterion e.g. 3 or more hives lasting 5 minutes or more, a single episode of vomiting, erythema, etc.
Data Collection – The FARRP/TNO Dataset

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FARRP/TNO Threshold Database
Methodological Approach

• Criteria for inclusion:
  - Published study or clinic files
  - Food-allergic by history or other factors
  - DBPCFC (open challenges for infants)
  - Description of NOAEL and/or LOAEL (if dosing regimen provided, then can determine NOAEL from LOAEL)
  - Data on individual patients
  - Objective symptoms @ doses
FARRP/TNO Threshold Dataset
Mining Existing Clinical Literature

• Individual NOAELs identified in some cases; discerned from LOAELs in other cases
• Individual LOAELs were available in many cases
• Data not available on all of the subjects from some studies because of method of reporting
• With interval-censoring survival analysis, both NOAEL and LOAEL are used to derive a “true” threshold value
LITERATURE REVIEW TOOL
TNO uses a literature review tool (developed in house) to keep track of published research and considerations whether or not the published research contains data of interest. The literature review tool contains all (potentially) relevant publications from 2011 onwards.

- ((allergy AND (food OR nutrition) AND (DBPCFC OR challenge OR provocation OR threshold OR eliciting)))

Additional custom searches done by FARRP, which can be imported in the tool.
LITERATURE REVIEW TOOL

FoodAllergy Website

Select a Project:

**Prevalence**
Project directed towards the prevalence of allergy

**Threshold**
Project directed towards the thresholds at which allergy occurs

**Not Available**

**Available**
Wainstein BK, Saad RA  
*Asia Pacific allergy* (2015)  
**Repeat oral food challenges in peanut and tree nut allergic children with a history of mild/moderate reactions.**

**BACKGROUND**  
In peanut and tree nut allergic children a history of anaphylaxis is associated with subsequent severe reactions.

**OBJECTIVE**  
We aimed to prospectively rechallenge peanut and tree nut allergic children with a history of mild/moderate reactions to assess their allergy over time.

**METHODS**  
In this cohort study peanut and tree nut allergic children with a history of mild/moderate reactions during a controlled oral challenge were invited to have a follow-up oral challenge to the same food at least 1 year later.
Repeat oral food challenges in peanut and tree nut allergic children with a history of mild/moderate reactions.

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LITERATURE REVIEW TOOL
STEP 2: READING FULL ARTICLE

Development and validation of a standardized double-blind, placebo-controlled food challenge matrix for raw hazelnuts.

Background
Double-blind, placebo-controlled food challenge (DBPCFC) is considered the gold standard for food allergy diagnosis. However, this test is rarely performed routinely in clinical practice because of various practical issues, e.g., the lack of a standardized matrix preparation. The aim of this study was to develop and validate a convenient DBPCFC matrix that can easily be implemented in daily clinical practice. The focus of this study was the blending of hazelnuts, whereby the hazelnuts retained as much as possible their allergenicity and could be mixed homogenously in low-doses to the matrices.

Methods
A basophil-activation test (BAT), microbial tests, and an LC-MS/MS test were performed to assess respectively the allergenicity of the used hazelnuts, the microbial stability of the novel developed matrices, and the homogeneity of the hazelnuts in the matrices. A sensory test was conducted to validate the blending of the hazelnuts in the matrices. A pilot DBPCFC study included eight patients as proof of concept.
LITERATURE REVIEW TOOL

STATISTICS

[Diagram showing statistics and analysis results]
LITERATURE REVIEW TOOL
FROM 2011 TO NOW

› > 2500 Titles and Abstracts reviewed
› > 570 Kept for full PDF review
› > 50 Identified as containing quantitative data in a usable format
Normalizing and Modelling Dose Distributions

- Normalize doses on basis of total protein from the food
- Use individual NOAELs and LOAELs
- Done by interval-censoring survival analysis using three probability distribution models (Log-Normal, Log-Logistic, and Weibull); now model averaging
Peanut Threshold Population Distribution (expressed as mg peanut protein)
<table>
<thead>
<tr>
<th>Source</th>
<th>Total No. of Peanut Allergic Individuals</th>
<th>ED_{10}</th>
<th>95% CI</th>
<th>ED_{05}</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nancy Data</td>
<td>286</td>
<td>14.4</td>
<td>10.7, 19.6</td>
<td>7.3</td>
<td>5.2, 10.4</td>
</tr>
<tr>
<td>Published Papers(^1)</td>
<td>164</td>
<td>14.1</td>
<td>6.6, 29.9</td>
<td>4.2</td>
<td>1.7, 10.1</td>
</tr>
<tr>
<td>Combined</td>
<td>450</td>
<td>12.3</td>
<td>9.0, 16.8</td>
<td>5.2</td>
<td>3.6, 7.4</td>
</tr>
</tbody>
</table>

\(^1\)Nine published studies yielded NOAELs and LOAELs for 164 peanut-allergic individuals. Twenty-one individuals from 3 papers (A, B, and D; See Taylor et al., 2009) were excluded from analysis to avoid potential duplication of individuals as these studies included individuals from the Nancy clinic.

All values reported in mg of whole peanut.
# VITAL® Reference Doses 2011-12

<table>
<thead>
<tr>
<th>Allergen</th>
<th>mg Protein Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut*</td>
<td>0.2</td>
</tr>
<tr>
<td>Milk*</td>
<td>0.1</td>
</tr>
<tr>
<td>Egg*</td>
<td>0.03</td>
</tr>
<tr>
<td>Hazelnut*</td>
<td>0.1</td>
</tr>
<tr>
<td>Soy*</td>
<td>1.0</td>
</tr>
<tr>
<td>Wheat*</td>
<td>1.0</td>
</tr>
<tr>
<td>Other Tree Nuts*</td>
<td>0.1</td>
</tr>
<tr>
<td>Sesame*</td>
<td>0.2</td>
</tr>
<tr>
<td>Crustacean shellfish*</td>
<td>10.0</td>
</tr>
<tr>
<td>Fish*</td>
<td>0.1</td>
</tr>
<tr>
<td>Mustard</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Existing Threshold Data for Allergenic Foods

• Human data on individual minimal eliciting doses on dozens to hundreds of individuals

• Data from the actual sensitive sub-population: food-allergic human subjects

• Data from controlled clinical oral challenges conducted by experienced medical professionals

• Known, small challenge doses
The BIG Question

• Are these data sufficient to establish population threshold doses that could be used by public health authorities to protect food-allergic consumers?

• If not, what data gaps exist and how do we go about filling those data gaps?
Questions on the Existing Dataset

• Do we have sufficient data on all commonly allergenic foods?
• Are the patients representative of the affected population?
• Do they include a sufficient number of the most highly sensitive/severely affected individuals?
• Do differences exist between patients with and without histories of severe reactions?
• Do differences exist between adults and children?
• Do geographic differences occur?
• Do differences occur between different clinic populations?
• How do you adjust for differences in clinical protocols?
• Does the form of the allergenic food make a difference?
Questions on the Existing Dataset

• Do we have sufficient data on all commonly allergenic foods? Except a few tree nuts
• Are the patients representative of the affected population? Yes
• Do they include a sufficient number of the most highly sensitive/severely affected individuals? Yes
• Do differences exist between patients with and without histories of severe reactions? No
• Do differences exist between adults and children? No
• Do geographic differences occur? No
• Do differences occur between different clinic populations? ??
• How do you adjust for differences in clinical protocols? OK
• Does the form of the allergenic food make a difference? No??
Table 4. ED$_{10}$ doses for whole peanut as assessed by the log-normal probability distribution model for severity grade.

<table>
<thead>
<tr>
<th>Severity Grade</th>
<th>Total No. of Peanut Allergic Individuals</th>
<th>ED$_{10}$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe$^1$</td>
<td>40</td>
<td>10.4</td>
<td>4.8, 22.6</td>
</tr>
<tr>
<td>Non-Severe$^2$</td>
<td>123</td>
<td>10.2</td>
<td>6.4, 16.1</td>
</tr>
<tr>
<td>No Prior History$^3$</td>
<td>123</td>
<td>27.0</td>
<td>17.4, 42.0</td>
</tr>
</tbody>
</table>

$^1$Severe reactions include three organ systems, asthma requiring treatment, laryngeal edema, and/or hypotension.

$^2$Non-severe reactions include one or two organ systems, abdominal pain, rhinoconjunctivitis, urticaria, eczema, non-laryngeal angioedema, and/or mild asthma (peak flow rate <80%)

$^3$History of prior allergic reactions and severity of reactions were not available. These individuals were identified as being sensitized to peanut by means of diagnostic tests.

All values reported in mg whole peanut
Questions on the Existing Dataset

• Uncertainty Factors
  - exercise
  - alcohol
  - medications
  - illnesses and general clinical health
  - stress
  - menstruation

• These factors exist for most chemical hazards in foods

• Risk management